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PTO/SB/01 (06-03)

P01936US06

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Attorney Docket Number

DECLARATION	FOR UTILI SIGN	ITOR	First Named Inve	entor	MARSH	ALL, William	E.			
PATENT A		N	COMPLETE IF KNOWN							
	FR 1.63)	<u>L</u>	Application Num	ber						
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Submitted OR With Initial		ed after Initial	Art Unit			<del></del>				
Filing		R 1.16 (e))	Examiner Name							
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I hereby declare that:										
Each inventor's residence, ma	ailing address, a	and citizenship are a	s stated below	next to the	neir name.					
I believe the inventor(s) name which a patent is sought on the			inventor(s) of t	he subjec	t matter wh	ich is claime	ed and for			
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		(Title of the	Invention)							
the specification of which										
is attached hereto										
OR			_							
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This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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to a collection of betweeness unless R display a valid OMB control number. Under the Paperwork Reduction Act of 1996, no persons are justified to r Application Number Filling Duty POWER OF ATTORNEY OR First Harried Inventor MARSHALL, William B. **AUTHORIZATION OF AGENT** Group Art Unit Exercises Name P01936US06 Attorney Doclar Number I hereby appoint: Place Customer 22885 ✓ Practitioners at Customer Numba Number Bar Code Label here Prectitioner(s) named below: Name Registration Number as my/our attorney(s) or agent(s) to projecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith. Please change the correspondence address for the above-identified application to: The above-mentioned Customer Number. OR Firm or Individual Name Address Address ZΙρ City Country Telephone FIEX I am the: Applicant/Inventor. Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTOISBI96). SIGNATURE of Applicant or Assignee of Record William E. Marahall Name

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NOTE: Signatures of all the inventors or sesignoss of jecord of the entire interest or their representative(s) are required. Submit multiple

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### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:

MARSHALL, William E.

SERIAL NO:

continuation-in-part of 09/883,550

FILED:

March 15, 2004

TITLE:

OLIGORIBONUCLEOTIDES ALERT THE IMMUNE SYSTEM

OF ANIMALS TO THE IMMINENCE OF MICROBIAL

**INFECTION** 

GRP./A.U.:

1645

EXAMINER:

CONF. NO.: DOCKET NO:

P01936US06

### 132 DECLARATION OF WILLIAM E. MARSHALL

Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

### Dear Sir:

I, William E. Marshall hereby declare the following.

- 1. I am the inventor on the above-identified case and am familiar with the prosecution including the office action dated January 20, 2004.
- 2. My background includes a Ph.D. in biochemistry from the University of Illinois, post-doctoral training at Uppsala University and Cambridge University, assistant professor of biochemistry at the University of Minnesota, director of technology development at General Foods Corp., president of the Microbial Genetics Division of Pioneer Hi-Bred International, member of the Iowa Academy of Sciences, chairman of the National Agricultural Research and Extension Users Advisory Board of the U.S. Congress, member of the advisory panel on biotechnology to the Office of Technology Assessment of the U.S. Congress, member of the advisory panel on intellectual property to the GATT, and associate professor of microbiology and immunology at the New York Medical College.

- 3. In 1989, as president of the Microbial Genetics Division of Pioneer Hi-Bred, Int'l., Inc. I submitted a New Animal Drug Application to the Center for Veterinary Medicine of the Food and Drug Administration. The results of the Phase III trial with a probiotic in a gel were very positive but the Agency required an explanation of the cellular and molecular modes of action before permitting claims that the drug had reduced the incidence of viral shipping fever in cattle 40%. I left industry and joined the faculty of the New York Medical College for the expressed purpose of determining the modes of action.
- 4. Our first discovery was learning that bacteria encountering physiologic conditions release substances that absorb ultraviolet light with a maximum at 254 nm.
- 5. Feeding or injecting preparations of the bacteria-free released substances <10kDa to mice protected them from the lethality of a subsequent challenge of endotoxin.
- 6. Third, I learned that the released substances were oligoribonucleotides (ORNs) from RNA.
- 7. I observed that bacteria begin to accumulate these oligoribonucleotides (ORNs) concomitantly with the destruction of their ribosomes late in their growth cycle. I reasoned that the oligoribonucleotides originated from the destruction of the ribosomes.
- 8. I further deduced that through co-evolution the immune system adapted a learned alert response to the sudden appearance of released oligoribonucleotides. This alert response protected the host from the lethality of endotoxemia.
- 9. It is well established that the immune system responds to molecules that are non-mammalian in nature and origin and, to which they have been exposed during coevolution. These molecules represent non-self. Ribosomes are ubiquitous in biology and contain sequences of RNA that are specific to their kingdoms, genera and species. I believe that the immune systems of animals have adapted a learned response, through coevolution, to the different oligoribonucleotides that arise from the destruction of ribosomes throughout the biological world.

I believe that the alert response, which protected mice from endotoxemic death that we described in earlier applications occurs when sentry cells of the immune network detect oligoribonucleotides found only, or at a disproportionately high level in the ribosomes of bacterial cells.

Since viruses do not contain ribosomes, the alert response to bacterial oligoribonucleotides has been evolutionarily adapted to include protection against viral infections, as seen in the clinical trial mentioned in paragraph 3, above.

- 10. An example of oligoribonucleotides that are unique or found in disproportionately high levels in bacterial cells are the ribosomal signature sequences which differentiate the three kingdoms of microbes and are also found uniquely in certain genera and species of bacteria. Woese, C.R., 2002, On The Evolution of Cells, Proc. Natl. Acad. Sci. 99(13):8742-7. Shaver, Y. et al., 2001 Variation in 16S-23S rRNA Intergenic Spacer Regions among *B. Subtilis* 168 Isolates. Molec. Microb. 42:101-10.
- 11. Another example is the ribosomal sequences encoded by DNA sequences that are present at levels 13 times higher in bacterial genomes than found in mammalian cells. These contain the sequence Cytosine-phosphate-Guanosine (CpG) between at least 4 or 5 adjoining bases on either side. A number of these oligodeoxynucleotides (ODNs) have been found by Kreig to activate cells of the immune system, but since ODNs are not released when bacteria enter physiologic conditions, the immune response is not a learned adaptation and their administration therefore induces adverse responses and toxicity. Kreig, A., et al., 1995 CpG Motifs in Bacterial DNA Trigger Direct B-cell Activation, Nature 374:546-9 and J Immun 1998 161:2428-34.

In my opinion, administering the oligo<u>ribo</u>nucleotides that are complementary to these oligo<u>deoxy</u>nucleotides would result in immune stimulation without adverse side effects. Some examples are:

AGAGGGUCGCACGCGGUA (SEQ ID NO: 1) and, CGUACUGCAACUCG (SEQ ID NO: 2) and, AGGUACAGCCAGGACUACGA (SEQ ID NO: 3).

12. I have found that the oligoribonucleotides that are effective immune stimulants were smaller than 10kDa, i.e., containing fewer than about 33 nucleotides. Furthermore, they could not be further reduced in size by the enzyme ribonuclease. To explain this resistance, the ORNs must be double stranded, hairpins, or have groups blocking the active site or contain unusual bases or nucleotide sequences.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: 3-12-04

William E. Marshall